REMARKS

Claim 1 has been amended to specify one embodiment of the present invention wherein the reaction portion is formed as a thin walled capillary having a closed end and a wall thickness of about 0.1mm. Claim 5 is amended, and claim 25 added, to specify the capillary tube is a glass capillary tube having an inner diameter of about 0.8 mm and an outer diameter of about 1.0 mm. Support for the amendment to claims 1, 5 and new claim 22 is found throughout the specification, and more particularly on page 54, lines 5-8. Claim 7 has been amended, and claim 20 added, to specify that the closed end of the reaction portion is formed to optimize optical transmissibility for light having a wavelength of about 400-800 mm to about 800 nm. Support for the amendment to claims 7 and 20 is found throughout the specification, and more particularly on page 54, lines 9-12, page 66, lines 23-25, page 68, lines 1-6 and original claim 16. Claim 7 is further amended to incorporate the limitation of original claims 8 and 14, and thus claims 8 and 14 are cancelled. Claim 19 is new, and support for the amendment is found throughout the specification and more particularly on page 19, lines 17-18.

New claims 21 and 22 are added to claim a further embodiment of the present invention. Support for new claims 21 and 22 is found throughout the specification, and more particularly on page 54, lines 5-12, and original claim 9. The remaining claim amendments are made to provide correct antecedent basis and provide clarity. The claim amendments add no new matter.

The present invention is directed to a sample container that has been designed to provide for the rapid and homogenous thermal cycling of the container contents. As noted at page 18, lines 4-7, "The response time for sample cooling [and heating] is very fast due to the use of thin walled glass capillary tubes for holding samples, ..." The ability to rapidly thermal cycle a sample allows one to conduct nucleic acid amplifications in a shorter length of time, and has been found to increase the yield and specificity of the polymerase chain

reaction relative to prior art methods. Furthermore, the containers of the present invention have been designed to allow real time monitoring of the amplification reaction by monitoring fluorescent emitted from the end tip of the container. As demonstrated in Fig. 22A, detecting fluoresence emitted from the end tip of the sample vessel provides a 10 fold increase in signal intensity relative to detecting fluoresecence emitted from the side of the container. Detection of real time fluorescence (i.e. during PCR) allows for the determination of when the complementary DNA strands have annealed or melted and thus allows for optimizing the annealing and denaturation incubation times and avoiding excessive incubation times.

Accordingly, the claimed sample vessels of the present invention incorporate several elements in a unique combination that allows applicants the ability to rapidly thermal cycle the sample vessel contents. The motivation for combining these separate and distinct elements derives solely from applicants' discovery of the beneficial results in yield and specificity (see data of Figs. 6, 7 and 9) produced by conducting such rapid cycling PCR.

Claims 1-3, 5-9 and 14-16 stand rejected under 35 U.S.C. § 102(b) as being anticipated by von Behrens (US 3,914,985). While applicants traverse this rejection, in an effort speed the prosecution of this matter, applicants have amended independent claims 1 and 7 to further distinguish the claimed invention over the prior art reference.

Claim 1 as amended herein specifies that the reaction portion is formed as a capillary having a closed end, and a wall thickness of 0.1mm. In one embodiment as specified in claim 5 the capillary tube has an inner diameter of about 0.8 mm and an outer diameter of about 1.0 mm. Accordingly, claims 1-6 specify that the reaction portion of the claimed container is defined by a very thin wall, wherein the walls are composed of a material that exhibits a high level of thermal conductivity. The thickness and composition of the vessel walls represent factors relevant to the speed at which the contents of the vessel can be heated and cooled by an external differential in temperature. The von Behrens reference is silent regarding the thickness of the walls of the disclosed sample vessels and is devoid of

any suggestion regarding the use of a thin walled capillary tube as a component of a sample container.

Independent claim 7 has been amended to specify that the reaction portion has a closed end, wherein the closed end is shaped to optimize optical efficiency. The Examiner has noted that the von Behrens' reference discloses that in instances where fluid exchange between the contents of the inner tube and the outer tube, "the lower end of the capillary section may be permanently sealed" (column 5, lines 63-65). However, applicants respectfully submit that the von Behrens' disclosed embodiment of sealing the end of a capillary tube to prevent fluid flow from the interior space of the capillary fails to teach a capillary tube having a closed end that is formed to optimize optical transmissibility. Accordingly, the invention of claim 7 and all claims depending form that claim (i.e. claims 9-12 and 14-18) is novel over the von Behrens reference.

Applicants respectfully submit the invention of claims 1-3, 5-9 and 14-16 is novel over the von Behrens reference. Accordingly, applicants request the withdrawal of the rejection of those claims as being anticipated by the von Behrens reference

Claims 1-4, 6-9 and 16-18 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Gerarde (US 3,518,804). While applicants traverse this rejection, in an effort speed the prosecution of this matter, applicants have amended independent claims 1 and 7 to further distinguish the claimed invention over the prior art reference.

Gerarde discloses a micropipette for receiving a predetermined quantity of liquid and subsequently transferring the liquid from the capillary space into a storage chamber attached to the capillary tube. Therefore the capillary of Gerarde performs the equivalent function as the receiving portion of the presently claimed invention. The storage chamber has a larger internal volume than the capillary tube portion. Therefore, Gerarde discloses a device wherein fluid is introduced into a capillary space and subsequently moved into a larger chamber. Accordingly, the capillary/receiving portion of Gerarde does not meet the limitation of the present claims that require the receiving portion to be larger than the

storage chamber/reaction portion. In the presently claimed sample container, fluid is introduced into a receiving portion and then moved to the reaction portion, wherein the receiving portion has an internal volume greater than that of the reaction portion.

The present claims require the capillary tube to be closed at one end and the only way fluid can be introduced into the reaction portion is through the receiving portion. Therefore, unlike the Gerarde device, fluids cannot be directly taken into the capillary space of the claimed sample container, but must first pass through the receiving portion. The Gerarde reference does disclose that the end of the capillary tube can be sealed, but only after the fluid has been taken up by the capillary and transferred to the storage chamber. Therefore, Gerarde fails to disclose an empty sample vessel that has a receiving portion larger than an attached reaction portion wherein the reaction portion is closed at the end opposite of where the receiving portion is attached to the reaction portion.

In addition the Gerarde reference fails to disclose a sample vessel having walls of only 0.1 mm in thickness. Nor does that reference teach a sample container that has a closed end, wherein the closed end is shaped to optimize optical efficiency. Accordingly, applicants respectfully submit the invention of claims 1-4, 6-9 and 16-18 is novel over the von Behrens reference, and applicants request the withdrawal of the rejection under 35 U.S.C. § 102(b) as being anticipated by Gerarde.

Claims10 and 11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over von Behrens. Applicants respectfully traverse the rejection.

Claims 1, 6, and 10, as amended herein specify both the inner diameter and the outer diameter of the container and thus specify the thickness of the container walls. As discussed in the specification on page 18, lines 4-15, the use of thin walled tubes is one element that allows for rapid thermal cycling of a sample contained within the container while maintaining a homogenous temperature through out the fluid sample.

The Examiner contends that while von Behrens is silent regarding the specific thickness of the capillary tube walls, it would obvious to the skilled practitioner to optimize

capillary dimensions based on the intended volumes of the samples to be used. First of all applicants note that while the inner diameter of the capillary tube may be relevant to the intended sample volume, the overall thickness of the capillary wall is not. Thus the intended volumes to be used with the von Behrens device do not provide any guidance as to the thickness of the capillary tube.

Furthermore, applicants note that the von Behrens device is designed for harvesting, compacting and measuring particulate matter. Since the von Behrens reference does not teach or suggest a use of their device that would require rapid thermal cycling of the contents of the capillary tube, there is simply no motivation to use thin walled containers as is required by amended claim 1 of the present invention. On the contrary, von Behrens makes repeated reference to the fragile nature of the inner tube (see column 3, lines 5-7; column 4, lines 67-68 and column 5, lines 2-4). Thus, von Behrens would motivate one to prepare capillary tubes having thicker walls rather than thinner ones to reduce the risk of breakage. Therefore, while the von Behrens reference never directly addresses the thickness of their capillary tubes, they provide no motivation for using thin walled tubes as part of a container as applicants have done and now claim in the present invention. Furthermore, applicants respectfully submit that the discussions within von Behrens regarding the fragility of their capillary tubes would provide motivation to prepare and use capillary tubes that have thicker, stronger walls. Accordingly, the von Behrens reference provides no teaching or suggestion to prepare a container comprising a thin walled reaction portion.

Applicants respectfully submit that claims 1 and 10 and all claims depending therefrom are patentable over the von Behrens reference and applications request the withdrawal of the rejection of claims 1 and 10 for obviousness over that reference.

Claims 4, 17 and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over von Behrens in view of Gerarde. Applicants respectfully traverse the rejection.

Claim 4 is dependant from claim 1 and therefore, this claim requires that the container comprises a thin walled reaction portion. As discussed above, the von Behrens reference fails to provide any guidance with regard to the thickness of the capillary walls. In fact, by stressing the fragility of the capillary component of their device, and providing no reason to prepare thin walled tubes (i.e. having a wall thickness of about 0.1), the reference actually teaches away from the presently claimed thin walled device of the present invention. The secondary Gerarde reference provides no additional teachings with regards to the use of thin walled capillaries. Accordingly, the combined teachings of the von Behrens and Gerarde references fail to teach or suggest the present invention.

Claims 17 and 18 are dependant from Claim 7. Claim 7 has been amended to specify that the reaction portion has a closed end, wherein the closed end is formed to optimize optical transmissibility. In one embodiment of the present invention it is desirable to conduct fluorescent monitoring of the sample in the containers of the present invention while the sample is being subjected to rapid thermal cycling. Experimental results have demonstrated (see data provided in Fig. 22A) that detecting fluoresence emitted from the end tip of the reaction portion provides a 10 fold increase in signal intensity relative to detecting fluoresecence emitted from the side of the container. Therefore, there is a benefit to forming the closed end of the reaction portion in a manner that optimizes optical trnamissibility, as is now explicitly stated in amended claim 7.

The Examiner has noted that both the von Behrens and Gerarde references disclose that the end of the capillary tube may be "sealed." In Gerarde the end of the capillary tube is sealed after fluid is introduced into the sample container. Furthermore, Gerarde discloses at column 4, lines 48-51:

> When transfer has been accomplished the capillary tip may be sealed, if desired, by flame heating at 34, in accordance with conventional practices. The tip may also be sealed by wax.

Applicants respectfully submit that such procedures while properly sealing the capillary tip would not produce a closed end, wherein the closed end is formed to optimize optical

transmissibility. Similarly, von Behrens also discloses that their capillary tube may be "sealed" to prevent fluid exchange between the contents of the inner and out tubes. More specifically, von Behrens discloses at column 7, lines 45-48:

> ... the lower end of the capillary section 12b is sealed with a flame or with a quantity 30 of standard sealing compound well known for use in sealing the ends of microhematocrit tubes...

The von Behrens reference fails to teach or suggest any use for their device that would require fluorescent monitoring of the capillary tube contents. Accordingly, there is no suggestion provided within the Gerarde or von Behrens references to form the end tip of the capillary in a manner that produces a closed end that optimizes optical efficiency. The methods of "sealing" the end tip as disclosed in Gerarde and von Behrens (flame heating, wax, sealing compound) would be expected to diminish the fluorescent signal emitted from the end of the capillary tube. The cited references provide no utility for a capillary tube that is "sealed" at one end in a manner that allows efficient optical transmission from the end tip of the capillary tube.

Applicants respectfully submit that amended claim 7 and all its dependencies are patentable over the cited references. Accordingly applicants request the withdrawal of the rejection of claims 4, 17 and 18 as obvious over the combined teaching of the von Behrens and Gerarde references.

Claim 12 stands rejected under rejected under 35 U.S.C. § 103(a) as being unpatentable over von Behrens in view of Hawes. Applicants respectfully traverse the rejection.

The Examiner contends that one of ordinary skill in the art would know to seal the end of a capillary tube of the primary reference for the known and expected result of providing an art recognized means of interfacing the end of the capillary tube with optical interrogation devices. However, applicants respectfully submit there was no motivation provided within the von Behrens reference that would direct one of ordinary skill to consider

the optical characteristics of their devices. The von Behrens reference is devoid of any suggestion that there device could be used with optical interrogation devices.

Applicants respectfully submit the von Behrens reference discloses several methods for "sealing" the open end of the capillary tube. There was simply no reason put forth within the von Behrens reference that would suggest to a skilled practitioner that the capillary end should be sealed in a manner that does not interfere with optical transmissibility from the tip of the capillary. Applicants respectfully submit that the motivation to provide a closed end that optimizes optical efficiency has been impermissibly derived from applicants new sample container, which in one embodiment is used with optical interrogation devices.

Furthermore, applicants respectfully submit that the vonBehrens reference cannot be properly combined with the Hawes reference. Hawes is directed to sample vessels for use in a laser-excited Raman spectrometer. As stated at column 2, lines 5-12:

> For one thing, when using short wavelength radiation for excitation, the Raman lines are masked somewhat by fluorescent radiation occurring in the sample and no one has yet found a practical way of distinguishing the fluorescent radiation from the Raman radiation. Such masking fluorescent radiation may even be generated by impurities in the sample.

and again at column 2, lines 26-27:

> This technique suffers from the disadvantage that large amount of fluorescent radiation are emitted by the material forming the wall of the cell.

Thus the Hawes reference clearly establishes that fluorescence emissions are undesirable for operation of a Raman spectrometer. Therefore, it is unlikely that one of ordinary skill in the art would consider the teaching of a reference relating to a laser-excited Raman spectrometer when designing a container comprising a closed end capillary tube wherein the end is optimized to detect fluorescence at a wavelength ranging from about 400 nm to about 800 nm.

Applicants respectfully submit that Hawes reference cannot be properly combined with von Behrens reference to render the present invention obvious. Accordingly,

applicants request the withdrawal of the rejection of claim 12 as being unpatentable over von Behrens in view of Hawes.

Claims 1-12 and 14-18 stand provisionally rejected for obviousness-type double patenting as being unpatentable over claims 19-27 and 34-39 of co-pending application serial number 10/914,648. Applicants hereby request this issue be held in abeyance until a determination of allowable subject matter has been made.

The foregoing claim amendments and remarks are believed to fully respond to the Examiner's rejections. The claims are believed to be in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance.

Respectfully submitted,

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